REMARKS

1. Discussion of Claim Amendments

Claims 62-78 and 80-107 are cancelled.

Clam 59 is amended as follows:

(1) "preventing" is replaced with "reducing risk of". (With basis on page 5, lines 26-28.)

(2) treatment of macular edema has been added (with basis at P22, L18);

(3) the active compound is limited to those defined by formula V, previously presented in claim 63, itself derived from original PCT use claim 7, with the variables R1, R3-R12 constrained with basis in original PCT claims 7-23 and pp. 8-15 of the specification (and more particularly, at page 11, lines 14-22; page 12, lines 22-24; page 13 lines 5-15 and page 14 lines 3, 5 and 7-9).

2. Enablement Issues (OA pp. 2-4)

The Examiner has rejected pending claims 59-61 and 63-78 on the ground that the application allegedly does not provide sufficient enablement for preventing diabetic retinopathy. The Examiner concedes that the description is enabling for treatment, but not prevention of non-proliferative diabetic retinopathy.

The Examiner explains at OA page 3, lines 5-14:

> The claims are very broad. Since the instant specification provides no limiting definition of the term "prevention", the term will be interpreted expansively. The term "prevention" might vary widely in meaning from "preventing" a disease from occurring to "preventing" it from progressing. Nor is the term limited by any time frame.

> The claims are thus very broad insofar as they suggest that one will not experience the disease when taking the claimed agent; that should one get the disease, it will not worsen, or that following its treatment, it will not recur. While such "prevention" might theoretically be possible under stoically controlled laboratory conditions, as a practical matter it is nearly impossible to achieve the "real world" in which patient live.

We have replaced the word "preventing" with "reducing risk of" to overcome the Examiner's rejection, and thus, we believe that the claims are now clear and enabled by the description.

3. Written Description Issues (OA pp. 4-5)

Claims 59-61 and 63-78 are also rejected for allegedly failing to comply with the written description content. The examiner states:

> The claims are drawn to using "at least one compound" or "prodrugs" being used for treating of preventing non-proliferative diabetic retinopathy. The specification discloses some compounds within the scope of what is claimed. However, there is no evidence that all the compound and their prodrugs being used for retinopathy were known to the applicant. Therefore, the artisan would not have accepted that applicant was in possession of the claimed method of use.

We have limited the present claim 59 to only relate to a narrow set of compounds described by the formula V. Thus, the compounds covered by the present claims are now clearly defined by a chemical structure.

Isotretinoin is included in the structural definition of the claimed compounds. The use of isotretinoin in methods of treatment is exemplified in detail in Example 1 to 4 of the description. Applicant is thus clearly in possession of at least one species (isotretinoin) by virtue of actual reduction to practice. See MPEP §2163(II), under heading "For Each Claim Drawn to a Single Embodiment or Species", clause (A).

In addition, Applicant is in possession of additional species (page 11, lines 14-22; page 12, lines 22-24; page 13, lines 5-15 and page 14 lines 3, 5 and 7-9; and cp page 14, line 15 to page 15, line 28, although the latter includes compounds not presently claimed) that are known chemical compounds (retinoids) named by the specification, for which the complete structures are known. See Clause (B) of the aforementioned passage of MPEP §2163(II).

As disclosed at P20, L10-12

"A large number of retinoids and other compounds to be used according to the invention are commercially available (e.g. from Signma-Aldrich Co., St. Louis, Mo., USA or from F. Hoffmann-LaRoche Ltd., Basel, Switzerland, etc.)."

Hence, many if not all of the identified compounds may also be considered actually reduced to practice in the sense that they have actually been made.

Amended claim 59 is a "genus" claim, and as stated by MPEP 2163 (II) under the heading "For each claim drawn to a genus",

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see

> i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Even if isotretinoin was the only "possessed" species, a single species can sometimes support a genus claim:

> There may be situations where one species adequately supports a genus. See, e.g., *Rasmussen*, 650 F.2d at 1214, 211 USPQ at 326-27 (disclosure of a single method of adheringly applying one layer to another was sufficient to support a generic claim to "adheringly applying" because one skilled in the art reading the specification would understand that it is unimportant how the layers are adhered, so long as they are adhered); *In re Herschler*, 591 F.2d 693, 697, 200 USPQ 711, 714 (CCPA 1979) (disclosure of corticosteroid in DMSO sufficient to support claims drawn to a method of using a mixture of a "physiologically active steroid" and DMSO because "use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description

only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description."); *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 285 (CCPA 1973) (the phrase "air or other gas which is inert to the liquid" was sufficient to support a claim to "inert fluid media" because the description of the properties and functions of the air or other gas segmentizing medium would suggest to a person skilled in the art that appellant's invention includes the use of "inert fluid" broadly.).

However, we respectfully submit that numerous compounds within the genus are not only identified but commercially available, and hence serve to provide written description basis for the genus.

In amended claim 59, R1, R4, R9, R10 and R12 are defined as CH3, and R3, R5, R6, R7 and R8 are defined as H.

Below is a list of compounds specifically named in the description and covered by claim 59.

Page 14:
Isotretinoin (13-cis-retinoic acid) (line 16)
11-cis-retinol (line 16)
11-cis-retinal (line 16)
11-cis-retinyl bromoacetate (line 17)
N-(4-hydroxyphenyl)-retinamide (Fenretinide) (line 17)
Retinaldehyde (line 18)
All-trans-retinyl bromoacetate (line 18)
All-trans-retinyl chloroacetate (line 18)
Retinoyl betaglucoronide (line 19)
13-cis-retinoic acid (line 23)
N-ethyl-13-cis-retinamide (line 23)
N-(4-hydroxyphenyl)-13-cis-retinamide (line 24)

All trans retinyl propionate is fully defined by P13, L12, although not "named" per se.

Below is a table showing examples of compounds for each of the different types of R11 mentioned in claim 59. These compounds are mentioned in the description at page 14, lines 15-19, or fully specified by P13, L12 in one case although not mentioned by name.

Compound name	-R11	Conformation
Isotretinoin	-COOH	13cis/(2Z,4E,6E,8E)
Retinol/Vitamine A	$-CH_2OH$	(2E,4Z,6E,8E)
11-cis-retinal	-CHO	(2E,4Z,6E,8E)
11-cis-retinyl bromoacetate	$-CH_2OCOCH_2BR$	(2Z,4E,6Z,8Z)
all-trans-retinyl chloroacetate	$-CH_2OCOCH_2Cl$	(2E,4E,6E,8E)
All-trans-Retinyl propionate (P13, L12)	$-COOCH_2CH_3$	(2E,4E,6E,8E)
Fenretinide	-CONH-4-hydroxyphenyl	(2E,4E,6E,8E)
All-trans-Retinoyl betaglucoronide	-COO-Beta-D-glucoronide	(2E,4E,6E,8E)

The examiner seems to interpret the WD requirement as requiring that "**all** of the compounds and their prodrugs that are within the scope of the claim --not just a representative number" - be "known to the applicant". But that is not the law.

4. Prior Art Issues (OA p. 5-7)

Claim 59, as amended, is directed to methods of reducing the risk of, or treating, non-proliferative diabetic retinopathy and/or macular edema. Hence, we begin the prior art analysis with a discussion of the nature of these conditions.

Diabetic retinopathy can be subdivided in two stages wherein the first comprises non-proliferative diabetic

retinopathy and the other is proliferative diabetic retinopathy.

1. Mild-Severe Diabetic Retinopathy or non-proliferative diabetic retinopathy: At the earliest stage, microaneurysms occur. They are small areas of balloon-like swelling in the retina's tiny blood vessels. As the disease progresses, blood vessels providing oxygen and nourishment to the retina are blocked thus depriving numerous areas of the retina of their blood supply, thus causing ischemia. Another symptom of non-proliferative or pre-proliferative diabetic retinopathy is the consequence of protein deposits (exudates) which may blur vision.

2. Proliferative Diabetic Retinopathy: At this advanced stage, signals sent by from the ischemic tissue trigger the growth of new blood vessels. This condition is called proliferative retinopathy and is characterized by angiogenesis, i.e. the growth of new blood vessels. These blood vessels are abnormal and fragile and grow along the retina and along the surface of the vitreous humor that fills the inside of the eye. These blood vessels do not cause symptoms or vision loss. However, their thin, fragile walls cause them to leak blood which may cause severe vision loss and even blindness.

Macular edema occurs when fluid and protein deposits collect on or under the macula of the eye. The swelling may distort a person's central vision, as the macula is near the centre of the retina at the back of the eyeball. This area holds tightly packed cones that provide sharp, clear central vision to enable a person to see form, color, and detail that is directly in the line of sight. Macular edema may be associated with retinal conditions in non-proliferative

diabetic retinopathy but is distinct from proliferative diabetic retinopathy.

4.1. "Claims 59-62 and" [sic, no other claims listed] are rejected as allegedly anticipated under 102(b) by Oikawa et al.

Oikawa et al. discloses that three synthetic retinoids (Re 80, Am 580 and Am 80) have anti-angiogenic effect in chorioallantoic membranes of growing chickens. The authors further speculate that these compounds could be used in the treatment of "angiogenesis-dependent" disorders, such as diabetic retinopathy. Thus, Oikawa et al. relates to proliferative diabetic retinopathy.

The synthetic retinoids mentioned in Oikawa et al. for treatment of "angiogenesis-dependent" disorders fall outside of the structural definition of the compounds mentioned in amended claim 59. Further, the document does not mention treatment of non-proliferative diabetic retinopathy or macular edema. Thus, the amended claims are new in view of Oikawa et al.

4.2. The Examiner asserts that the current application names joint inventors and advice of the obligation to point out the inventor dates of each claim that is not commonly owned.

According to both the cover sheet of the PCT pamphlet and the inventor declaration filed on July 11, 2007, there is only one inventor for all claims. Thus we believe we have fulfilled our obligation, and do not need to further specify the ownership of the claims.

4.3. Claims 59-61, 63-70 and 108-115 stand rejected as obvious over Campochiano in view of Oiwaka.

The claims of the present invention have been amended to relate to a method of treating nonproliferative diabetic retinopathy and/or macular edema.

Oikawa et al:

Oikawa et al. discloses that the synthetic retinoids (Re 80, Am 580 and Am 80) have anti-angiogenic effect in chorioallantoic membranes of growing chickens. The authors speculate that these compounds could be used in the treatment of "angiogenesis-dependent" disorders, such as diabetic retinopathy. Thus Oikawa et al. only relates to proliferative diabetic retinopathy, which is not the same medical condition as non-proliferative diabetic retinopathy and macular edema. As stated above, the compounds disclosed in Oikawa et al. fall outside of the definition of compounds in amended claim 59. Further, the document does not relate to treatment of the same medical condition as non-proliferative diabetic retinopathy and macular edema. A person skilled in the art would therefore not find reasons to consider the disclosures in Oikawa et al. relevant for the present invention, and thus the present invention has inventive step over Oikawa et al.

Campochiaro et al:

Campochiaro et al. describes a method for treating the disease proliferative vitreoretinopathy (PVR) which is the most common complication of a retinal detachment (RD), and occurs in approximately 8-10% of patients who develop an RD. Proliferative vitreoretinopathy is a disease characterized by proliferation of retinal pigment epithelial cells, which are normally found on the posterior surface of the retina, typically as a consequence of traumatic or degenerative injury to the retina that leads to formation of a hole in the retina,

detachment of the retina, and dispersion of retinal pigment epithelial cells into the vitreous cavity and onto the anterior surface of the retina. The proliferating retinal pigment epithelial cells exert their detrimental effect mainly by spreading over the anterior and/or posterior surfaces of the retina where these cells cause stiffening, contraction and detachment of the retina. Proliferative vitreoretinopathy is an independent disease entity which is described separately from diabetic retinopathy in reference textbooks and original science communications.

Thus, treatment of vitreoretinopathy is treatment of a disease different from non-proliferative diabetic retinopathy or macular edema. Furthermore, since the two diseases have different pathogenesis and pathology the mere fact that a compound may be used for treating vitreoretinopathy does not teach the skilled person that the same compound may be used for treating another different disease, the two diseases being morphologically distinct. Accordingly, the invention as claimed in the present claims exhibits inventive step.

In conclusion, the present invention is novel and inventive over Oikawa et al. and Campochiaro et al., taken alone or in combination.

Respectfully submitted,

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